REMARKS

In the Office Action mailed January 22, 2009, claims 33-36 were rejected under 35 U.S.C. §112, second paragraph, for the reasons set forth in the Detailed Action section of the Office Action.

By the foregoing proposed claim amendments to claims 33-36, Applicants have addressed the deficiencies which gave rise to the rejection of these claims under 35 U.S.C. §112, second paragraph, and Applicants now believe that this ground for rejecting these claims has been rendered moot.

Turning now to the prior art based rejections, claims 1-6 and 22-32 have been rejected under 35 U.S.C. §103(a) as being unpatentable over *Tamura et al.* and *Smith et al.*

Claims 1-11 and 22-32 have been rejected under 35 U.S.C. §103(a) as being unpatentable over *Tamura et al.* and *Smith et al.* in view of *Nguyen.*

Claims 1-15 and 22-32 have been rejected under 35 U.S.C. §103(a) as being unpatentable over *Tamura et al.* and *Smith et al.* in view of *Nguyen* and *Hubbell et al.* Claims 1-11 and 16-32 have been rejected under 35 U.S.C. §103(a) as being unpatentable over *Tamura et al.* and *Smith et al.* in view of *Nguyen* and *Kuhla et al.*

For the following reasons, Applicants traverse these prior art based grounds for rejecting the claims of the application under 35 U.S.C. §103(a).

Subject of the Invention

The present invention is directed to a compound based on hyaluronic acid (HA), wherein alcohol groups of hyaluronic acid are esterified with rhein as such or in derived form, or

a salt thereof as set forth in claim 1, and to related processes, pharmaceutical compositions, medicinal products and devices, biomaterials, and methods according to the present invention.

In particular, the claimed compound according to the present invention presents the following unexpected, advantageous properties:

- Avoiding the drawbacks associated with oral administration of rhein;
- Long-term shelf stability as compared to HA alone (in particular, no hydrolytic degradation), as is documented under Example 5, 1);
- Increased syringeability as compared to HA alone, as documented under Example 5, 2);
- Increased protective effect against IL-1 induced MMP expression as compared to either rhein or HA alone (synergetic effect between rhein and HA moities), as documented under Example 7.

The patentability of the present invention is supported by experimental data as presented in Examples 1 to 7.

Rejection of Claims 1-6 and 22-32

Concerning the Examiner's rejection of claims 1-6 and 22-32 on the ground of obviousness under 35 U.S.C. 103 (a) over *Tamura et al.* (EP 1082963) and *Smith et al.* (*Arthritis & Rheum., 1999*) please consider the following.

a. *Tamura et al.-EP 1082963*

Tamura et al. is directed to conjugates of hyaluronic acid (HA), a derivative thereof or a salt thereof, and a therapeutic agent, for joint diseases. In particular, *Tamura et al.* aims at conjugates of a therapeutic agent for joint diseases and hyaluronic acid, a derivative thereof or a salt thereof, which would be capable to localize and retain hydroxamic acid in a joint cavity.

Tamura et al. is further directed to a method for preparing such a conjugate, which comprises binding a site of a therapeutic agent for joint diseases that does not affect the activity of the agent (e.g., amino group, a carboxyl group, a hydroxyl group, a thiol group, or the like) to a carboxyl group, a hydroxyl group, or a functional group at the reducing end of hyaluronic acid, a derivative thereof or a salt thereof [0057], [0072], [0073]. *Tamura et al.* generally describes the possibility of activating the above sites either on a therapeutic agent or on the hyaluronic acid, a derivative thereof or a salt thereof, to form various types of bonds such as amide bond, ester bond, thioester bond, ether bond, imino bond, sulphide bond, etc. [0073], to form the conjugate.

When *Tamura et al.* specifically disclose the activation of a carboxyl group, they broadly and generally disclose the activation of this group either on a therapeutic agent for joint diseases or on HA, an HA derivative, or a salt thereof, with the use of a dehydrative condensation agent (such as carbodiimides, phosphoniums, uroniums, and the like) to form an amide bond, an ester bond, or a thioether bond [0075]. Furthermore, *Tamura et al.* fail to guide the ordinarily skilled person to choose "a site of a therapeutic agent for joint diseases that does not affect the activity of the agent" to attach HA.

Tamura et al. generally states that the mode of administration of the conjugate disclosed herein is not particularly limited or suitable for any administration route, including oral route [0086].

In addition, *Tamura et al.* teaches in the direction of using a HA conjugate where HA is conjugated with a therapeutic agent. In *Tamura et al.*'s conjugate, HA plays the role of a vehicle for the therapeutic agent with the aim of retaining the said therapeutic agent with the hydroxamic acid in a joint cavity to prolong the drug action at this specific site.

Contrary to the Examiner's assertions on page 3 of the Office Action mailed January 22, 2009, *Tamura et al.* fails to specifically teach the attachment of a therapeutic agent to HA, a hydroxyl group, through the activation of a carboxylic group in the therapeutic agent.

Furthermore, as acknowledged by the Examiner, *Tamura et al.* fails to guide the ordinarily skilled person towards the use of a specific therapeutic agent for joint diseases, in particular rhein for the preparation of a conjugate [0034].

At most, *Tamura et al.* discloses metalloproteinase inhibitors (in particular hydroxamic acids, i.e., compounds chemically completely different from rhein) as a specific therapeutic agent category for joint diseases for the preparation of a conjugate.

Tamura et al. does not address in any way shelf stability or syringeability of HA, or anticipate a potential synergetic effect between the HA drug carrier and the conjugated drug.

Therefore, Applicants respectfully assert that *Tamura et al.* does not anticipate or render obvious the claimed invention.

b. *Smith et al.*

Smith et al. is directed to a study on the effect of diacerhein on early stages of damage in a canine model of osteoarthritis (OA), when administered by oral route. Oral diacerhein is said to show a slowing down effect on the progression of OA at early stages of the damage. However, *Smith et al.* disclose that diacerhein does not have a significant effect at later stages of OA.

Smith et al. further disclose the absence of reduction in collagenase activity (metalloproteinase) in OA cartilage following diacerhein treatment (p. 553, col. 2).

Smith et al. disclose that during the four-week treatment dogs suffered loose stools, a side effect of oral administration of diacerhein and rhein also mentioned in the present application (see p. 1, [0005], as originally filed).

Smith et al. fail to teach any other administration route than oral route for diacerhein.

Smith et al. fail to teach any combination of diacerhein with any another agent, such as HA.

Therefore, Applicants respectfully assert that *Smith et al.* does not anticipate or render obvious the claimed invention.

Furthermore, when reading *Tamura et al.* in combination with *Smith et al.*, the ordinarily skilled person would have no guidance at all nor incentive to select any particular site of conjugation on a therapeutic agent for joint diseases, with a specific site of HA, to form a conjugate.

In particular, the ordinarily skilled person would not have any incentive to particularly select rhein or a derived form, or a salt thereof, as a therapeutic agent for joint diseases to form a conjugate for joint disease treatment.

Furthermore, *Smith et al.* fail to palliate the deficiencies of the teachings of *Tamura et al.* To the contrary, when reading *Smith et al.*, the person ordinarily skilled in the art would be taught that diacerhein lacks inhibitory effect on collagenase activity (metalloproteinase) in OA, and lacks significant effect at later stages of OA.

Tamura et al. and *Smith et al.*, taken separately or in combination, do not provide any teaching whatsoever of the present invention and its advantageous properties. Therefore, Applicants respectfully assert that claims 1-6 and 22-32 are not anticipated by or rendered obvious by *Tamura et al.* and *Smith et al.* taken separately or in combination.

Rejection of Claims 1-11 and 22-32

Concerning the Examiner's rejection of claims 1-11 and 22-32 on the ground of obviousness under 35 U.S.C. 103 (a) over *Tamura et al.* (EP 1082963) and *Smith et al.* (*Arthritis & Rheum., 1999*) in view of *Nguyen et al.* (US 5,612, 321) please consider the following.

a. *Tamura et al.-EP 1082963*

Tamura et al. fail to render claims 1-6 and 22-32 obvious as discussed above. Further, *Tamura et al.* fail to teach a process according to claims 7-11.

Therefore, Applicants respectfully assert that *Tamura et al.* does not render the claimed invention obvious.

b. *Smith et al.*

Smith et al. fail to render obvious claims 1-6 and 22-32 as discussed above. Further, *Smith et al.* fail to teach a process according to claims 7-11.

Therefore, Applicants respectfully assert that *Smith et al.* does not render the claimed invention obvious.

c. *Nguyen et al. –US 5,612, 321*

Nguyen et al. relate to polysaccharides (including HA or crosslinked HA) grafted to antioxidants on at least one hydroxyl group of the polysaccharide. *Nguyen et al.* aim at generating polysaccharides with increased resistance to hydroxyl radicals by grafting them with antioxidants.

Nguyen et al. do not teach a compound according to present claim 1. Further, *Nguyen et al.* do not teach the preparation of a conjugate of rhein or a derived form, or a salt thereof, nor the preparation of a conjugate through a process according to present claim 7.

The process disclosed in *Nguyen et al.*, which the Examiner cited (Example 6), relates to the grafting of HA to an antioxidant by reacting an ammonium salt of HA with 3,5-di-t-butyl-4-hydroxybenzoyl chloride in the presence of NMP (polar solvent) and ammonium ion, exchanging the resulting product to sodium salt in aqueous solution.

Further, when reading *Nguyen et al.*, the ordinarily skilled person would have no incentive to replace the antioxidants by rhein for conjugation with HA.

Therefore, contrary to the Examiner's assertions on page 5 of the Office Action, *Nguyen et al.* fail to specifically teach a process according to claim 7.

Therefore, the Applicants respectfully assert that *Nguyen et al.* does not render the claimed invention obvious.

Furthermore, *Nguyen et al.* fail to palliate the deficiencies of the teachings of *Tamura et al.* and *Smith et al.*

Therefore, based on the above reasons, Applicants respectfully assert that claims 1-11 and 22-32 are not rendered obvious by *Tamura et al.*, *Smith et al.* or *Nguyen et al.* taken separately or in combination.

Claims 1-15 and 22-32

Concerning the Examiner's rejection of claims 1-15 and 22-32 on the ground of obviousness under 35 U.S.C. 103 (a) over *Tamura et al.* (EP 1082963) and *Smith et al.* (*Arthritis & Rheum., 1999*) in view of *Nguyen et al.* (US 5,612, 321) and *Hubbell et al.* (US 5,834,274), please consider the following.

a. *Tamura et al.-EP 1082963*

Tamura et al. fail to render obvious claims 1-15 and 22-32 as discussed above.

Therefore, Applicants respectfully assert that *Tamura et al.* do not render the claimed invention obvious.

b. *Smith et al.*

Smith et al. fail to render obvious claims 1-15 and 22-32 as discussed above.

Therefore, the Applicants respectfully assert that *Smith et al.* reference does not render the claimed invention obvious.

c. *Nguyen et al. –US 5,612, 321*

Nguyen et al. fail to render obvious claims 1-11 and 22-32 as discussed above. Further, as acknowledged by the Examiner, *Nguyen et al.* fail to teach the preparation of a HA conjugate in a non polar aprotic solvent in the presence of a hydrogen ion acceptor according to the present invention.

d. *Hubbell et al. – US 5,834,274*

Hubbell et al. relate to methods of coating and/or encapsulating surfaces and three-dimensional objects with cross-linked networks of water soluble polymers. *Hubbell et al.* discloses methods for polymerization of macromers using visible or long wavelength ultraviolet light to encapsulate or coat either directly or indirectly living cells or tissues with polymeric coatings.

First, *Hubbel et al.* deals with encapsulation and coating technologies that are far remote from the field of the present invention.

Further, *Hubbell et al.* fail to teach the preparation of a conjugate of HA.

Hubbell et al. do not teach a conjugate of rhein or a derived form, or a salt thereof, nor the preparation of a conjugate of the invention through a process according the invention, either.

The Examples 1 and 2 from *Hubbel et al.* cited by the Examiner are directed to the synthesis of PEG acrylates (diacrylate and tetraacrylate), which are far remote from the present invention.

Furthermore, *Hubbel et al.* fail to palliate the deficiencies of the teaching of *Tamura et al.*, *Smith et al.* and *Nguyen et al.*

Therefore, based on the above reasons, Applicants respectfully assert that claims 1-11 and 22-32 are not rendered obvious by *Tamura et al.*, *Smith et al.*, *Nguyen et al.* and *Hubbel et al.* taken separately or in combination.

Claims 1-11 and 16-32

Concerning the Examiner's rejection of claims 1-11 and 16-32 on the ground of obviousness under 35 U.S.C. 103 (a) over *Tamura et al.* (EP 1082963) and *Smith et al.* (*Arthritis & Rheum., 1999*) in view of *Nguyen et al.* (US 5,612, 321) and *Kuhla et al.* (US 4,788,187) please consider the following.

a. *Tamura et al.-EP 1082963*

Tamura et al. fail to render obvious claims 1-15 and 22-32 as discussed above. Further, *Tamura et al.* fail to teach acid chloride of rhein and a process for preparation thereof.

Therefore, Applicants respectfully assert that *Tamura et al.* reference does not render the claimed invention obvious.

b. *Smith et al.*

Smith et al. fail to render obvious claims 1-15 and 22-32 as discussed above. Further, *Smith et al.* fail to render obvious an acid chloride of rhein and a process for preparation thereof.

Therefore, Applicants respectfully assert that *Smith et al.* does not render the claimed invention obvious.

c. *Nguyen et al. –US 5,612, 321*

Nguyen et al. fails to render obvious claims 1-15 and 22-32 as discussed above.

Further, *Nguyen et al.* fail to teach the preparation *of* an acid chloride of rhein. In particular, *Nguyen et al.* fails to teach the preparation of an acid chloride of rhein comprising preparing a suspension of rhein in an aprotic non-polar solvent, and adding an amount of SOCl2 so as to obtain a molar ratio between SOCl2 and rhein greater than 10.

Therefore, the Applicants respectfully assert that *Nguyen et al.* does not render the claimed invention obvious.

d. *Kuhla et al. – US 4,788,187*

Kuhla et al. relate to benzocyclobutene aminoalkylene ether and thioether compounds and their use in gastrointestinal disorders.

Kuhla et al. do not render obvious a conjugate of rhein or a derived form or a salt thereof nor the preparation of a conjugate of through a process according the present invention, either.

The Example 2 from *Kuhla et al.* cited by the Examiner is directed to the synthesis of a benzocyclobutene derivative (5-(3-aminopropoxy)-1-(1-piperidinylmethyl)benzocyclobutene), which is far remote from the present invention.

Therefore, Applicants respectfully assert that *Kuhla et al.* does not render the claimed invention obvious.

Furthermore, *Kuhla et al.* fail to palliate the deficiencies of the teaching of *Tamura et al.*, *Smith et al.* and *Nguyen et al.*

Therefore, based on the above reasons, Applicants respectfully assert that claims 1-11 and 16-32 are not rendered obvious by *Tamura et al.*, *Smith et al.*, *Nguyen et al.* and *Hubbel et al.* taken separately or in combination.

For all these foregoing reasons, Applicants respectfully request entry of the foregoing claim amendments, reconsideration of the present Application in light thereof, and in light of the foregoing remarks, and then allowance of all claims 1-36, as amended, over all the prior art of record.

Respectfully submitted,

By: _____

Clifford W. Browning
Reg. No. 32,201
Krieg DeVault LLP
One Indiana Square, Suite 2800
Indianapolis, IN 46204
(317) 238-6203